MFps/Fes displayed numerous aberrant vascular structures in the yolk sac and defects in cardiovascular and craniofacial development. These and other results suggest that constitutive MFps/Fes activity in the absence of normal Flk1 signaling leads to exuberant vasculogenesis/angiogenesis. Finally, Haigh and colleagues demonstrate that MFps/Fes expression in *Flk1* null or heterozygous ES cells results in an increase in migratory behavior of mesodermal cells in vivo and a 5- to 10-fold increase in hemangioblast development in vitro. Though no direct interaction between Flk1 and Fps/Fes was demonstrated, the results of the study suggest that Fps/Fes may play a role downstream of VEGF-A/Flk1 signaling and/or complement a parallel signaling pathway.

One surprising result was that MFps/Fes expression failed to rescue hematopoietic development in the *Flk1* null ES cells. The authors suggest that a more detailed evaluation may indicate some level of rescue that was missed in the current study. As vascular smooth muscle cells are also derived from Flk1-expressing cells, future studies may also wish to address whether MFps/Fes rescues this lineage in *Flk1* null ES cells.

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von Willebrand factor: polymorphism predicts prompt polypeptide proteolysis

von Willebrand factor (VWF) has at least 3 important hemostatic roles: (1) bound to collagen, it captures platelets from rapidly flowing blood at sites of vessel wall injury; (2) it is able to cross-link platelets during aggregation, particularly at sites of high fluid shear stress; and (3) it serves as a carrier for coagulation factor VIII, which it delivers to the sites of enzyme complex assembly when it binds platelets. VWF is synthesized in only 2 tissues, endothelial cells and megakaryocytes, and in both it is either secreted constitutively or stored in specialized granules, the Weibel-Palade bodies or α-granules, respectively, from which it is released when the cells are stimulated. This large polypeptide (2791 residues before cleavage of the 741-residue propolypeptide) first forms dimers in the endoplasmic reticulum through a C-terminal disulfide bond. In the Golgi, the dimers attach to each other through disulfide bonds near their N-termini, forming concatamers of potentially enormous length. These large multimers, called ultra-large VWF (ULVWF), are abnormally reactive by all measures of VWF activity, including their ability to bind platelets and collagen.[1,2] When released into the plasma, however, ULVWF multimers are rapidly processed to smaller, less-reactive forms through the action of the plasma protease ADAMTS-13, a reaction that somehow stops short of completely degrading VWF. ADAMTS-13 cleaves a site within the VWF A2 domain, 1 of 3 tandem A domains. The other 2, A1 and A3, bind platelet glycoprotein Ibα and collagen, respectively. Unlike A1 and A3, however, A2 is not enclosed within a disulfide loop, which may allow access to the cleavage site to be regulated by shear stress, thereby providing a mechanism to limit the extent of VWF proteolysis. Failure of VWF proteolysis due to congenital or acquired ADAMTS-13 deficiency underlies a severe and potentially catastrophic disorder, thrombotic thrombocytopenic purpura (TTP).[3]

In this issue of *Blood,* Bowen and Collins (page 941) describe a polymorphism within the A2 domain that increases VWF's susceptibility to proteolysis in plasma, with all evidence pointing to ADAMTS-13 as the responsible protease. It is curious that these investigators found the polymorphism while investigating a patient with type I von Willebrand disease (VWD), a disorder caused by global reduction in VWF levels, affecting multimers of all sizes. This patient had a normal pattern of VWF multimers in her plasma but displayed accelerated VWF proteolysis when her cryoprecipitate was incubated with cryo-poor plasma, a source of ADAMTS-13. The single nucleotide change (A to G) converts Tyr1584 to Cys at a site 21–amino acids N-terminal to the ADAMTS-13 cleavage site, and appears responsible for the enhanced susceptibility to proteolysis. The gain of a Cys residue within A2 is of interest and may explain the association of the variant with increased VWF proteolysis, given the recent finding that plasma disulfide reductase activity, in addition to proteolysis, may reduce the size of VWF by reduction and may enhance its proteolysis.[4]

The clinical consequences of this polymorphism are unclear. It is yet not determined whether the polymorphism is widespread or ethnically restricted. Nevertheless, its association with a more severe bleeding phenotype in a patient with type I VWD suggests that it can enhance the tendency to bleed when in the setting of other hemostatic defects. It is also possible that the polymorphism could ameliorate the effects of ADAMTS-13 deficiency, with carriers being spared the full spectrum of TTP. Finally, polymorphisms that moderately increase the susceptibility of VWF to proteolysis may modulate the tendency to thrombosis in other instances in which platelet thrombi are major contributors—in myocardial infarction and stroke, for example.

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1. Furlan M. Von Willebrand factor: molecular size and functional activity. Ann Hematol. 1996;72:341-348.
2. Fischer BE, Kramer G, Mitterer A, et al. Effect of multimerization of human and recombinant von Willebrand factor on platelet aggregation, binding to collagen and binding of coagulation factor VIII. Thromb Res. 1996;84:55-66.
3. Moake JL. Thrombotic microangiopathies. N Engl J Med. 2002;347:589-600.
4. Xie L, Chesterman CN, Hogg PJ. Control of von Willebrand factor multimer size by thrombospondin-1. J Exp Med. 2001;193:1341-1349.

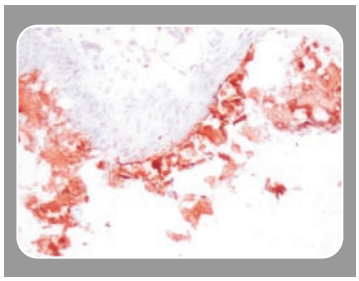
NF-κB activation in atherosclerosis: a friend or a foe?

Atherosclerosis is an inflammatory disease of the arterial wall that carries an important socioeconomic burden. The severe clinical manifestations of atherosclerosis (myocardial infarction, stroke) are mainly due to the

abrupt obstruction of the vessel lumen by a thrombus formed on the contact of a ruptured or eroded atherosclerotic plaque. The available data strongly suggest that immuno-inflammatory–related mechanisms are the major determinants of plaque complications. Therefore, most of the important advances in the comprehension of the mechanisms of atherosclerosis have come from studies aimed at elucidating the critical components involved in the modulation of the immuno-inflammatory balance within the plaque. However, despite the increasing knowledge regarding the role of inflammation in atherogenesis, the precise intracellular transduction pathways involved in this process remain largely unexplored.

Recent studies have pointed to the transcription factor nuclear factor κB (NF-κB) as potentially one of the most important proinflammatory pathways in atherogenesis. Various risk factors for atherosclerosis, including hypercholesterolemia, diabetes and its associated advanced glycation end products, hypertension, elevated plasma homocysteine levels, and increased oxidative stress, which is common to all the preceding conditions, are important activators of NF-κB. Activated NF-κB has been identified in smooth muscle cells, macrophages, and endothelial cells of human atherosclerotic lesions,[1] and enhanced activation of this transcription factor has been shown to occur very early following a high-fat, cholate-free diet in low-density lipoprotein receptor (LDLR)–deficient mice.[2] However, apart from significant positive correlations between activated NF-κB and proatherogenic activity, the direct role of NF-κB in the development and composition of atherosclerotic plaques had not yet been assessed.

In a recent study, Kanters et al, using LDLR-deficient mice with a macrophage-restricted deletion of IκB kinase 2 (IKK2) leading to specific inhibition of NF-κB activation in macrophages, reported the unexpected finding of increased atherosclerotic lesion formation and inflammation.[3] This result was associated with a significant reduction in the anti-inflammatory and anti-atherogenic cytokine interleukin-10 (IL-10), suggesting that a certain level of NF-κB activation was required for the control of the inflammatory reaction and the protection against unabated inflammatory and proatherogenic responses. This is in agreement with studies showing a central role for NF-κB in the induction of "protective" anti-apoptotic and anti-inflammatory genes, critical to the resolution of the inflammatory process.[4]



However, according to the study by Kanters and colleagues in this issue of *Blood* (page 934), the detrimental effect of NF-κB inhibition in atherogenesis depends on how NF-κB activity is inhibited. In this study, Kanters et al examined the effects of hematopoietic NF-κB1 (p50) deficiency in the development of atherosclerotic lesions in LDLR knockout mice. Instead of promoting the formation of larger inflammatory lesions, as was the case with IKK2 deficiency, a significant decrease in lesion size in mice with NF-κB1 deficiency, despite enhanced accumulation of T and B lymphocytes within the lesions, was observed. This could be explained, at least in part, by the observation that, in contrast to IKK2 deficiency, NF-κB1 deficiency did not lead to an alteration of the inflammatory balance in favor of a proatherogenic phenotype. Despite increased tumor necrosis factor (TNF) expression by NF-κB1$^{-/-}$ macrophages, other major proatherogenic molecules such as monocyte chemoattractant protein-1 (MCP-1) were down-regulated, whereas critical antiatherogenic factors such as IL-10 were significantly up-regulated. Decreased MCP-1 production and increased IL-10 expression may have contributed to limitation of plaque size despite enhanced accumulation of T cells. Another plausible mechanism leading to inhibition of lesion development in NF-κB1–deficient animals could be attributed to a potential defect in the uptake of oxidized low-density lipoprotein (oxLDL) by macrophages, as characteristic foam cells were absent in NF-κB1$^{-/-}$ lesions and both scavenger receptor class A (SR-A) expression and uptake of oxLDL were significantly reduced in NF-κB1$^{-/-}$ macrophages upon ex vivo stimulation with lipopolysaccharide (LPS). Whether this in vitro effect, observed following LPS stimulation, is relevant to the in vivo situation remains to be determined.

NF-κB appears to be at the crossroads of the inflammatory response in atherosclerosis, fine-tuning the response of the vessel wall to injury. Kanters et al should be commended for these provocative studies on the role of NF-κB, one of the most important proinflammatory transcription factors, in atherosclerosis.

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1. Brand K, Page S, Rogler G, et al. Activated transcription factor nuclear factor-kappa B is present in the atherosclerotic lesion. J Clin Invest. 1996; 97:1715-1722.
2. Hajra L, Evans AI, Chen M, Hyduk SJ, Collins T, Cybulsky MI. The NF-kappa B signal transduction pathway in aortic endothelial cells is primed for activation in regions predisposed to atherosclerotic lesion formation. Proc Natl Acad Sci U S A. 2000;97:9052-9057.
3. Kanters E, Pasparakis M, Gijbels MJ, et al. Inhibition of NF-kappaB activation in macrophages increases atherosclerosis in LDL receptor-deficient mice. J Clin Invest. 2003;112:1176-1185.
4. Lawrence T, Gilroy DW, Colville-Nash PR, Willoughby DA. Possible new role for NF-kappaB in the resolution of inflammation. Nat Med. 2001;7:1291-1297.

Memory depending on an intimate relationship

Accumulating evidence suggests a critical role for interleukin-15 (IL-15) in the development and maintenance of CD8 memory T cells. Nevertheless, there are some unsolved issues as to how IL-15 acts on target cells. Based on in vitro studies, it was postulated that nonlymphoid cells secrete IL-15, and T/natural killer (NK) cells expressing all 3 IL-15 receptor (IL-15R) components (α, β, and γ chain [γC]) bind it and proliferate.